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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,265	10/27/2003	Rima Kaddurah-Daouk	MBZ-001CP	4692

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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/695,265	KADDURAH-DAOUK ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *91-93 and 95-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *91-93 and 95-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/06, 11/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of claims 91-93 and 95-97 in the reply filed on June 16, 2006 is acknowledged.

Status of Application, Amendments, and/or Claims

2. Upon response to the restriction requirement, Applicants cancelled claims 1-90, 94 and 98-139. Claims 91-93 and 95-97 are currently pending and under examination.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 91 and 92 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7,005,255 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 91 and 92 are drawn to methods of correlating small molecules to various disease states. Claim 1 of U.S. Patent No. 7,005,255

B2 is drawn to a method of correlating small molecules to the specific disease of ALS. The patented claims are a species of the instant claims.

4. Claims 91 and 92 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/301077. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 91 and 92 are drawn to methods of correlating small molecules to various disease states. Claim 1 of copending Application No. 11/301077 is also drawn to a method of correlating small molecules to various disease states.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 91 and 92 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/301078. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 91 and 92 are drawn to methods of correlating small molecules to various disease states. Claim 1 of copending Application No. 11/301078 is also drawn to a method of correlating small molecules to various disease states.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 91 and 92 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/301079. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 91 and 92 are drawn to methods of correlating small molecules to various disease states. Claim 1

of copending Application No. 11/301079 is also drawn to a method of correlating small molecules to various disease states.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 91-93 and 95-97 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 11/357732. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 91-93 and 95-97 are drawn to methods of correlating small molecules to various disease states. Claim 1 of copending Application No. 11/357732 is also drawn to a method of correlating small molecules to various disease states.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 91 and 92 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/405033. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 91 and 92 are drawn to methods of correlating small molecules to various disease states. Claim 1 of copending Application No. 11/405033 is also drawn to a method of correlating small molecules to various disease states.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112 -Enablement

9. Claims 91-93 and 95-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for determining the presence of or predisposition for any disease based on a small molecule profile. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method for diagnosing the presence or predisposition to any disease based on a small molecule profile of a subject. The invention is in a class of inventions which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass diagnosing the presence of or predisposition for any disease associated with the small molecule profile of a subject.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large as it is highly unpredictable what

diseases can be diagnosed in the context of a vast database of diseases using a metabolic profile. Further identification of diseases will be by a trial and error method because the effects of diseases on metabolites or small molecules of the physiological system cannot be readily deduced even where the metabolic pathways are known. Each disease has unknown and unpredictable effects on metabolic function, and no general method for a priori selection of disease diagnosis is presented. Finally, establishing a standard small molecule profile for the plethora of known diseases would require a large amount of experimentation involving the testing of thousands of animals for thousands of diseases which if successful would then require additional testing in humans. This kind of Edisonian experimentation likely will require years to yield meaningful data for reliable and accurate diagnosis of a single disease let alone the vast number of diseases currently encompassed by the instant claims. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to diagnosis of disease using small molecule profiles. In a post filing publication (published in 2004, 2 years after the filing date of the instant application), Kell discusses the importance of making sense of raw metabolomic data and teaches deconvoluting raw metabolomic data can mean providing a chemical identity for metabolites reproducibly recognized as being present as judged by for example their retention index and mass spectrum. Kell teaches "spectrum to structure" has not been adequately attacked and needs automating since in plants some 80% of metabolites recognized by mass spectrometry have mass spectra that do not appear in the standard libraries (see p. 298 under Making sense of raw metabolomic data lines 1-8 and p. 299 first full paragraph). Additionally, Kell teaches that while NMR data is somewhat better the spectrum to structure problem remains an important component of making sense of the data and that it is hard to argue that we understand a metabolic system when we do not even know what most of its metabolites are (see p. 299

first full paragraph). Kell teaches this in reference to plant metabolites and plants are markedly less complex organisms than humans. Kell goes on to emphasize, on p. 299 col. 2 the existing problem of reconstructing metabolic networks. Kell discusses the ostensible size of the natural metabolome and teaches many organisms can and will metabolize xenobiotics for non nutritional purposes making the potential size of the potential metabolome practically infinite. Again this is in reference to plants. Kell teaches the genomic data can provide a baseline of reactions which are more or less known but there does not currently exist organism specific database which house this information. Additionally, the yeast model which currently exists provides an underestimate of metabolites because of imperfect knowledge, the lack of specificity among enzymes and the production of substances at very low concentrations that are not routinely detected. Kell goes on to say a human model is imminent (see p. 299 col. 2). At the time of filing no standard metabolome existed (and as of 2004 one still did not exist) with which to compare a disease state metabolome, making it impossible to diagnose a disease state by comparison to a standard "human metabolome." In the current case, where no standard small molecule profiles exist for any of the vast number of known human diseases it is entirely unpredictable what diseases if any can be accurately diagnosed by analysis of human metabolic profiles.

Working Examples

The specification has no working examples that provide evidence of accurate definitive diagnosis of a disease based on a small molecule profile

Guidance in the Specification.

The specification provides no specific or substantial guidance for diagnosing the presence of or predisposition to any possible disease based on a small molecule profile. Further no data is provided to evidence that it is possible to definitively and accurately diagnose a disease (from a database of all possible diseases) in an individual based on that individual's small molecule profile.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the lack of working examples or data evidencing the diagnosing of disease based on small molecule profiles balanced only against the high skill level in the art, it is the position of the Examiner that it would require undue experimentation for one of skill in the art to perform the method of the claims as broadly written.

Claim interpretation

10. The preamble of claim 91 recites "facilitating the diagnosis" while the final method step recites "thereby diagnosing the disease state." For the purpose of art rejections the claims are interpreted as a method of correlating a small molecule profile with the presence of any specific disease state.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 91-93 and 95-97 are rejected under 35 U.S.C. 102(b) as being anticipated by Siman (USPN 5,871,712, 02/16/1999).

Siman teaches (claim 91) a method for metabolomically facilitating the diagnosis of a disease of a subject, comprising:

obtaining a small molecule profile of a subject suffering from a subject having a disease (see col. 2 lines 1-7, where the subject has a nervous system disorder and SEQ ID NOs 1 and 2 comprise 7 amino acids which have the molecular weights of 1004 and 991 Daltons, respectively, and therefore meet the claim limitation of small molecule which is defined in the specification as molecules with a molecular weight of less than 2000 Daltons); and

comparing the small molecule profile to a standard small molecule profile thereby, facilitating diagnosis of the nervous system disorder (see col. 2 lines 8-12, 50-54).

With regard to claim 95, Siman teaches the subject is human (see col. 2 line 49).

With regard to claim 96, Siman teaches the subject is suffering from a disease state (see col. 2 lines 1-7, where the disease state is a nervous system disorder).

With regard to claim 97, Siman teaches the subject is suffering from a neurological disorder (see col. 2 lines 1-7).

Siman teaches the method steps of claim 92 comprising:

obtaining a small molecule profile of a subject suffering from a subject having a disease (see col. 2 lines 1-7, where the subject has a nervous system disorder and SEQ ID NOs 1 and 2 comprise 7 amino acids which have the molecular weights of 1004 and 991 Daltons, respectively, and therefore meet the claim limitation of small molecule which is defined in the specification as molecules with a molecular weight of less than 2000 Daltons); and

comparing the small molecule profile to a standard small molecule profile (see col. 2 lines 8-12, 50-54).

12. Claims 91, 92 and 95-97are rejected under 35 U.S.C. 102(e) as being anticipated by Niebroj-Dobosz et al. (*Acta Neruol Scand*, July 1999).

Niebroj-Dobosz et al. teach (claim 91) a method for metabolomically facilitating the diagnosis of a disease of a subject, comprising:

obtaining a small molecule profile of a subject suffering from a subject having a disease (see p. 6 the abstract, where the disease is a nervous system disorder and Glutamate, aspartate, glycine and GABA are amino acids which have the molecular weights of 147, 133, 75 and 105.13 Daltons, respectively, and therefore meet the claim limitation of small molecule which is defined in the specification as molecules with a molecular weight of less than 2000 Daltons); and

comparing the small molecule profile to a standard small molecule profile thereby, facilitating diagnosis of the nervous system disorder (see p. 6 abstract).

With regard to claim 95, Niebroj-Dobosz et al.teach the subject is human (see p. 7 col. 1 lines1 under patients).

With regard to claim 96, Niebroj-Dobosz et al. teach the subject is suffering from a disease state (see p. 6 the abstract, where the disease state is Amyotrophic lateral sclerosis).

With regard to claim 97, Niebroj-Dobosz et al. teach the subject is suffering from a neurological disorder (see p. 6 the abstract, where the disease state is Amyotrophic lateral sclerosis).

Niebroj-Dobosz et al. teach the method steps of claim 92 comprising:

obtaining a small molecule profile of a subject suffering from a subject having a disease (see p. 6 the abstract, where the disease is a nervous system disorder and Glutamate, aspartate, glycine and GABA are amino acids which have the molecular weights of 147, 133, 75 and 105.13 Daltons, respectively, and therefore meet the claim limitation of small molecule which is defined in the specification as molecules with a molecular weight of less than 2000 Daltons); and

comparing the small molecule profile to a standard small molecule profile (see p. 6 abstract).

13. Claim 93 is rejected under 35 U.S.C. 102(e) as being anticipated by Kaser et al. (USPN 6,168,933 B1).

Kaser et al. teach a method for metabolomically predicting a subjects response to a therapeutic agent comprising:

obtaining a small molecule profile from the subject (see col. 15 line 45 to col. 16 line 24 and col. 11 lines 40-44, and col. 13 lines 1-10).

comparing the small molecule profile of the subject to a known standard established for the agent as an indication of whether the subject would benefit from treatment with the therapeutic agent (see col. 15 line 45 to col. 16 line 24).

Summary

14. No claims were allowable.

Correspondence

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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